REMARKS

Due to an inadvertent error, this application was incorrectly designated as Attorney Docket Number 3117-080. The Examiner is respectfully requested to correct the PTO file to indicate the correct Attorney Docket Number which is 3117-081.

Claims 90-91 and 93-97 are currently pending in the application, claims 1 and 92 having been canceled by amendment herein.

I. Objection and Rejection Under Section 112

The specification has been objected to and claim 92 has been rejected under 35 U.S.C. §112 as not providing support for the invention as claimed. In particular, the Examiner states that the specification as filed does not support the "conjugates of S. pneumoniae serotype 6A . . . although use of serotype 6 occurs."

Applicants do not agree and respectfully direct the Examiner's attention to Example 11 at pages 50-51 of the specification. Particularly demonstrated in Table 15 on page 51, are cross-linked immunogenic conjugates in which the capsular polymer is that of S. pneumoniae serotypes 3, 6A, 12, 14 and 23. In view of such teaching and exemplification, it is submitted that this objection is in error and should be withdrawn. Moreover, as indicated above, by amendment herein, claim 92 has been canceled without prejudice. Thus, it is further submitted that this rejection has been obviated and should be withdrawn.

II. Rejections Based on Section 102 or 103

A. Section 102 Rejection Based on Jennings

Claims 1, 90 and 96 have been rejected under 35 U.S.C. §102(e) as anticipated by U.S. Patent No. 4,356,170 to Jennings (Jennings). The Examiner states

that Jennings teaches conjugates of "capsular polymers from bacterial pathogens such as streptococci, pneumococci or meningococci" and that such conjugates "would inherently possess at least two carbonyl groups" citing to Jennings at col. 3-5, particularly lines 15-22 and 42-51.

Applicants respectfully disagree and submit that the presently claimed invention is in no way anticipated by Jennings and, in fact, is clearly contrary to the teachings of Jennings. Examiner's attention is directed to the presently pending claims 90-91 and 93-97. As clearly recited in all the pending claims, the present invention is an cross-linked immunogenic conjugate which is the reductive amination product of a capsular polymer of Streptococcus pneumoniae having at least two carbonyl groups directly covalently linked, through the carbonyl groups to a bacterial toxin or toxoid.

Examiner's attention is directed further to the teaching of the present specification at page 8, line 25 through page 9, line 2; see also Example 11 at pages 50-51. As explained therein, because the capsular polymer employed in the presently claimed conjugates have at least 2 carbonyl groups, conjugation of such polymers according to the method of the present invention results in cross-linked compositions. The cross-linked conjugate compositions are prepared by covalently attaching the reducing end groups of a capsular polymer obtained from S. pneumoniae, to amine groups of a bacterial toxin or toxoid.

In complete contrast to the presently claimed cross-linked conjugates, the Jennings reference describes antigenic conjugates in which a capsular polymer is attached via a terminally introduced aldehyde group to an amine group of tetanus toxoid. The method of attachment is asserted to be specific in that the only covalent attachment between the toxoid and the capsular polysaccharide occurs at the single terminally located

aldehyde group of the polysaccharide (Jennings, at col. 3, lines 55-63; see also, id. at col. 2, lines 34-38. The reference further asserts that the method of coupling employed "avoids cross-linking" between the polysaccharide and the protein. Jennings at col. 2, lines 38-39; see also, id. at col. 3, lines 62-63. In addition, as clearly recited in the claims of the Jennings patent, the conjugates prepared as taught therein are "non-cross-linked" conjugates. E.g., independent claims 1 and 11.

Applicants emphatically point out that the Examiner's assertion that the conjugates of Jennings "would inherently possess at least two carbonyl groups" is completely erroneous. The Jennings reference teaches conjugation via a single aldehyde group on the end of the polysaccharide. The clear focus of Jennings is to generate a single aldehyde group. This is accomplished by Jennings by pretreatment of the capsular polymer or polysaccharide which otherwise would yield more than one aldehyde, so that upon treatment with periodate, only one aldehyde is obtained. See, Jennings at col. 3, lines 10-17, 22-27, and at col. 4, lines 49-59 (pretreatment of the meningococcal group A polysaccharide).

In addition, Jennings also teaches mild oxidation of the polysaccharide in order to selectively form only a single terminal aldehyde group. Jennings at col. 3, lines 28-39. See Jennings, at col. 5, lines 38-54 which specifically teaches mild periodate conditions so as to produce only a single aldehyde on the polysaccharides of meningococcal C group. See also, col. 6, lines 5-9.

Thus, there is no affirmative teaching in Jennings concerning cross-linking. Rather, the only teaching in Jennings about cross-linking is a very negative view which clearly teaches away from cross-linking.

In view of the very real, clear differences between the presently claimed cross-linked conjugates and non-cross-linked conjugates described by Jennings, it is submitted that this reference does not and, in fact cannot, anticipate the present claims. Thus, this rejection must be withdrawn.

B. Section 103 Rejection Based on Jennings

Claims 91-95 have been rejected under 35 U.S.C. §103 as obvious in view of Jennings. The Examiner acknowledges that Jennings "does not particularly exemplify the use of capsular polymers of the particularly claimed serotypes"; however, the Examiner alleges that "use of the particular serotype polymer in the conjugate of Jennings et al. would have been prima facie obvious" in view of Jennings disclosure of the "use of any bacterial source including streptococci or pneumococci with the expected benefit of making the immunogen specific for the serotypes."

Applicants do not agree and respectfully submit that this rejection is plainly in error as a matter of fact and law. As explained more fully above in Section II A, in complete contrast to the presently claimed cross-linked conjugates, the conjugates disclosed by Jennings are non-cross-linked. In fact, as further detailed above, Jennings teaches that a single terminal aldehyde group is introduced into a capsular polymer by means of controlled mild oxidation and is attached to an amine of tetanus toxin in a process designed particularly to avoid cross-linking of the products formed. Thus, it is clear that instead of suggesting the presently claimed cross-linked conjugates, Jennings, in fact, teaches away from the presently claimed subject matter.

As the Court of Appeals for the Federal Circuit has made emphatically clear, where a reference teaches away from the claimed invention, such reference in no

way evidences the obviousness of such invention, but rather, is highly probative of and serves as a foundation for the legal conclusion of non-obviousness of such invention. E.g.; Raytheon Co. v. Roper Corp., 724 F.2d 957, 961 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984); accord, Dow Chemical Co. vs. U.S., 18 U.S.P.Q.2d 1657, 1662 (Ct. Cl. 1990); In re Hedges, 783 F.2d 1038, 1041 (Fed. Cir. 1986).

In view of the above remarks it is respectfully submitted that in the present situation, Jennings, rather than suggesting the present invention, suggests just the opposite and thus cannot support the present rejection based on Section 103. Hence, this rejection must be withdrawn.

C. Section 103 Rejection Based on Jennings and Uchida

Claim 97 has been rejected under 35 U.S.C. §103 in view of Jennings in combination with Uchida et al., 1972, Science 115:901-03 (Uchida). The Examiner states that it would have been prima facie obvious to "substitute CRM 197 of Uchida et al. in the immunogenic conjugate of Jennings et al. since CRM 197 is a functional equivalent to diphtheria toxin of Jennings."

Applicants respectfully disagree. For reasons detailed above, it is submitted that Jennings in no way suggests, much less, teaches the presently claimed cross-linked conjugates. Uchida adds nothing to the Jennings reference to make such conjugates obvious. Uchida merely describes two non-toxic proteins produced by Corynebacterium diphtheriae. These non-toxic proteins, designated CRM 45 and CRM 197, cross-react with diphtheria anti-toxin. Thus, the Uchida reference merely shows that the toxoid employed in one embodiment of the present invention, i.e., CRM 197, exists. Nothing in this reference suggests that this toxoid should be coupled to capsular

polymers, much less to a capsular polymer to form a cross-linked conjugates as presently claimed.

In view of the above, it is respectfully submitted that this rejection is in error and should be withdrawn.

D. Section 103 Rejection Based on Anderson II Anderson III and Anderson and Clements

Claim 92 has been rejected under 35 U.S.C. §103 as obvious in view of U.S. Patent No. 4,761,283 to Anderson (Anderson II), U.S. Patent No. 4,762,713 to Anderson (Anderson III) and U.S. Patent No. 4,808,700 to Anderson and Clements (the Anderson and Clements patent). The Examiner states that these references "disclose and/or claim immunogenic conjugates between capsular polymer fragment and bacterial toxin or toxoid carrier", although they do not show the use of a capsular polymer fragment for S. pneumoniae serotype 6A. The Examiner concludes that it would have been obvious to substitute the polymer fragments of serotype 6A in view of the "broad disclosure" of the cited references.

Applicants again do not agree; however, as indicated above, claim 92 has been canceled without prejudice. Accordingly, it is submitted that this rejection is moot and should be withdrawn.

E. Provisional Section 103 Rejection Based on the Anderson and Clements Application

Claim 92 has been provisionally rejected under 35 U.S.C. §103 as obvious in view of the Anderson and Clements Application. The Examiner asserts that based on the earlier effective filing date the Anderson and Clements Application, if patented, would

be available under 35 U.S.C. §102(e). Again, Applicants do not agree; however, since claim 92 has been canceled without prejudice by amendment herein, it is submitted that this rejection has ben obviated and should be withdrawn.

III. Double Patenting Rejections

Claims 1 and 90-97 have been rejected under the judicially created obviousness-type double patenting as unpatentable over the following:

(1) U.S. Patent No. 4,673,574 to Anderson (Anderson I), claims 1-44 and 50;

(2) U.S. Patent No. 4,761,283 to Anderson (Anderson II), claims 1-27, 30 and 31;

(3) U.S. Patent No. 4,808,700 to Anderson and Clements (Anderson and Clements), claims 1-8;

(4) U.S. Patent No. 4,902,506 to Anderson and Eby (Anderson and Eby I), claims 1-32; and

(5) U.S. Patent No. 5,097,020 to Anderson and Eby (Anderson and Eby II), and claims 1-34.

In addition, claims 1 and 90-96 have also been provisionally rejected under the judicially created obviousness-type double patenting as unpatentable in view of claims 1-3, 15-28, 34-44 and 50 of Application Serial No. 07/205,132 by Anderson and Clements (Anderson and Clements Application) which is a continuation of the above Anderson and Clements patent. The Examiner asserts that the "other issued patents and the copending application claim species of the conjugates which are generically claimed in the instant application".

Attorneys for Applicants submit that these rejections are clearly improper.

Obviousness-type double patenting is a doctrine intended to prevent improper timewise extension of the patent right by prohibiting the issuance of claims in a second patent which are not "patentably distinct" from the claims of a first patent to the same inventor or owned by a common assignee. E.g., In re Braat, 937 F.2d 586, 592 (Fed. Cir. 1991).

As explained by the Court of Appeals for the Federal Circuit, when considering a double patenting rejection, the relevant inquiry is to compare the presently claimed subject matter with what was claimed in the first of the two patents and not what was disclosed in the specification of the first. In re Kaplan, 789 F.2d 1574, 1579 (Fed. Cir. 1986). Thus, the claims of the first patent must be compared with those of the application to determine whether they both are directed to the same invention or even a "mere variation of that invention which would have been obvious to those of ordinary skill in the relevant art." 784 F.2d at 1580. Further, the Kaplan Court stated emphatically, that "there must be clear evidence to establish why the variation would have been obvious which can properly qualify as 'prior art'." Id. (emphasis added).

Based on a comparison of the relevant claims, it is clear that the subject matter of the claims of the present application is not an obvious variant of that of the cited claims of the cited Anderson I, Anderson II, Anderson and Eby I, Anderson and Eby II combined with those of the Anderson and Clements patent. With respect, Applicants submit that the Examiner has overlooked and failed to appreciate the most critically important feature of the presently claimed invention. As detailed above in Section IIA, the presently claimed invention, is a cross-linked immunogenic conjugate. The cross-linked immunogenic conjugates comprise reductive amination products of (1)

the capsular polymer of a Streptococcus pneumoniae serotype having at least two carbonyl groups, covalently attached to (2) a bacterial toxin or toxoid. According to the present specification, at least two carbonyl groups, which provide for cross-linking of the capsular polymer with the protein moiety, are generated by treatment of the capsular polymer with an oxidizing agent. As explained further, the present conjugates having a lattice or network structure, provide "extremely high levels of anti-capsular polymer antibodies in infants." Abstract at lines 14-17. Additionally, the cross-linked conjugates comprise an intact capsular polymer of an S. pneumoniae serotype, rather than a capsular polymer fragment. The present claims are directed to compositions in which an intact capsular polymer is attached to a toxin or toxoid resulting in a cross-linked conjugate. None of the cited Anderson or Anderson/Clements patents suggest, much less teach, use of intact capsular polymers.

The claims of Anderson I, as well as Anderson II, which are directed to immunogenic conjugates in which a capsular polymer fragment is covalently attached, via a reductive amination process, to a bacterial toxin or toxoid do not suggest the present claims. The claims of Anderson I require specifically that the capsular polymer fragment have a chain length of 10-30 monomeric units and be derived from the capsular polymer of S. pneumoniae or H. influenzae. The claims of Anderson II require that the capsular polymer fragment be derived from H. influenzae type b, E. coli, Neiseria meningitis and S. pneumoniae and that the toxin is CRM 197. The claims of Anderson and Eby I and Anderson and Eby II are directed to conjugates, which like the presently claimed conjugates are cross-linked conjugates. Unlike the presently claimed conjugates, however, the conjugates of Anderson and Eby I and II require a capsular polymer fragment. In particular, the claims of Anderson and Eby I, require that the capsular

polymer fragment have a chain length of 10-30 monomeric units and be derived from the capsular polymer of S. pneumoniae or H. influenzae. The claims of Anderson and Eby II require that the capsular polymer fragment be obtained by a process entailing two steps, i.e., treating a capsular polymer with acid, base or enzyme to fragment the polymer and generating at least 2 carbonyl groups by treating with an oxidizing agent. Finally, the claims of Anderson and Clements require that capsular polymer fragment be attached to a novel non-toxic LT-BNT subunit of the heat labile enterotoxin of E. coli.

The present claims, in contrast, are directed to cross-linked immunogenic conjugates which comprise reductive amination products of (1) a intact capsular polymer of S. pneumoniae, having at least two carbonyl groups, obtained by treating said capsular polymer with an oxidizing agent, covalently attached to (2) a bacterial toxin or toxoid.

Nothing in the claims of the cited patents, alone or in combination, would have suggested the presently claimed conjugates. Moreover, nothing in the claims of the cited combination of patents would have established why the claimed conjugates would have been obvious. This falls far short of the test for obviousness-type double patenting as enunciated by the Court of Appeals in In re Kaplan, which emphatically held that "there must be some clear evidence to establish why the variation would have been obvious which can properly qualify as 'prior art'." 789 F.2d at 1580.

If, however, contrary to Applicants' reasoning above, the Examiner persists, Applicants would be amenable to submit a terminal disclaimer by the common assignee of the subject matter of this present application over Anderson I and II and Anderson and Eby I and II. More than such terminal disclaimer is certainly not necessary.

With respect to the provisional rejection based on the Anderson and Clements Application, Applicants respectfully submit, that for reasons detailed above with respect to the claims of the Anderson and Clements patent, this rejection is in error and should be withdrawn.

For the above reasons, these rejections based on obviousness-type double patenting should be withdrawn.

IV. Requirement Under 37 C.F.R. §1.78

The Examiner asserts that Anderson I, Anderson II and the Anderson and Clements Application would form a basis for a rejection under 35 U.S.C. §103 if these "commonly assigned" applications were available as prior art under 35 U.S.C. §102(f) and (g) and the applications were not commonly owned at the time the presently claimed invention was made. Thus, under 37 C.F.R. §1.78(c), the Examiner has required the "common assignee" to either show the conflicting inventions were commonly owned at that time or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement is stated to result in a holding of abandonment of the present application.

In order to be fully responsive to the Examiner's requirement under 37 C.F.R. §1.78(c), the Assignee of the present application which is a "common assignee" with the Anderson I and Anderson II patents, but not with the Anderson and Clements Application provides herewith a statement averring that the presently claimed invention was made subsequent to the invention claimed in the Anderson I and II patents as well as subsequent to that claimed in the Anderson and Clements Application. At present, the

statement is not executed. Attorneys for Applicants will forward an executed copy of the statement to the Examiner as soon as they have obtained the same.

Attorneys for Applicants, however, emphatically insist that the present claims do not conflict with those of the Anderson I and Anderson II patents (or for that matter, with the Anderson and Clements Application) because even if the Anderson I and Anderson II patents and the Anderson and Clements Application were available as prior art under 35 U.S.C. §102(e), (f) or (g), the presently claimed invention is not rendered unpatentable under 35 U.S.C. §102 and/or 103 because the presently claimed cross-linked conjugates of an intact capsular polymer are patentably distinct from the subject matter disclosed in these patents and the patent application. No interference should be declared because there is no interference in fact.

For the reasons above, it is submitted that Applicants have fully responded to this Examiner's requirement.

V. CONCLUSION

In view of the above amendments and remarks, it is submitted that the present claims are in form for allowance and early action to that end is respectfully requested.

Respectfully submitted,

S. Leslie Misrock Reg. No. 31,232

By Geraldine Lucas Bard

Date April 14, 1993

18,872

S. Leslie Misrock (Reg. No.)
PENNIE & EDMONDS
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090